Just go with the flow

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There are reasons to pursue the study of myocardial blood flow and its alterations in patients with rheumatic diseases (RDs) not the least of which is the fact that cardiovascular (CV) disease is a leading cause of morbidity and mortality in patients with RDs. Findings in RDs include endothelial dysfunction, arterial stiffness, and accelerated atherosclerosis. For example, Mehta et al. identified 3603 subjects with severe psoriasis in the U.K. General Practice Research Database and compared cardiovascular outcomes to a control group (4 subjects for each psoriasis subject) of 14,330 individuals from the same database.¹ They found that the adjusted hazard ratio for CV mortality was 1.57 in those with severe psoriasis compared to controls. The risk was independent of conventional risk factors. The adjusted relative risk of CV mortality was age related, RR 2.7 for a 40yo patient with severe psoriasis compared to a 1.9 for a 60yo patient with severe psoriasis. The same group also showed that the risk of CV mortality in patients with mild psoriasis was no different than that of the controls. In a meta-analysis of patients with rheumatoid arthritis, Avina-Zubieta et al. concluded that there was a 68% increase in the risk of myocardial infarction and stroke with RR of 1.93 and 1.67 in women and men, respectively. Furthermore, there was an 87% increase in the risk of congestive heart failure in patients with RA.² In addition, it appeared that patients with RA presented with more multivessel disease at the time of their initial diagnosis of CAD compared to matched controls in a case-control study done in Olmsted County, Minnesota.³ The impact of RDs on coronary events was

independent of traditional risk factors. Survival probability was lower for patients with CAD and rheumatoid arthritis than for those with CAD and no RA.

RDs are characterized by autoimmunity and inflammation, and the now accepted role of inflammation in both the development of coronary plaque and the instability of coronary plaque⁴ has led to increased interest in the RDs as models of inflammation and plaque development. Understanding the mechanisms by which inflammation participates in the early and more severe appearance of CAD and in the development of HFpEF may inform our approach to the mitigation of atherosclerotic diseases and heart failure in patients with and without RDs.

One line of investigation into the effects of RDs on vascular biology has been the study of myocardial blood flow (MBF). Multiple modalities have been used to study MBF in patients with RDs, including coronary doppler velocity with transthoracic echo, PET tracer kinetics with ¹³NH₃, ⁸²Rb, and ¹⁵O water and MRI contrast kinetics.

However, it must be said at the outset that MBF, especially hyperemic MBF, and myocardial or coronary flow reserve, MFR or CFR, may be affected by a variety of factors that can confound the interpretation of results and which are difficult or impossible to control especially in retrospective studies. Table 1 is a partial list of the factors that have been identified that can alter MBF. So, one must be cautious entering those waters, so as not to reach conclusions that will not hold up to independent confirmation.

Those precautions notwithstanding, Weber et al., in this issue of *the Journal*,⁵ present a retrospective study of 62 consecutive patients studied with ¹³NH₃ or ⁸²Rb PET MPI over a 13-year period. All data were acquired on a PET/CT system with a 64-slice CT scanner that allowed for semi-quantitative estimation of the extent and severity of coronary artery calcification. Control patients included 112 individuals selected using propensity score matching.

Resting MBF was similar in the two groups. Hyperemic flows were also similar in the two groups, 2.0 ± 0.4 vs 2.2 ± 0.7 ml/min/gm in patients and controls. However, despite similar average resting and hyperemic flows, the MFR was statistically lower in the

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Table 1. Factors that may influence myocardial blood flow

Age	Atherosclerosis ± stenosis
Gender	LV systolic dysfunction
BMI	Chronic kidney disease
Heart rate	HIV
Blood pressure	ACE inhibitors
LV contractility (dP/dT)	Beta blockers
Hypertension without LVH	Calcium channel blockers
Myocardial hypertrophy	Nitrates
Metabolic syndrome	Statins
Insulin resistance	Anti-inflammatory medications
Diabetes	Caffeine
Smoking	Vitamin C

psoriasis group at 1.92 ± 0.65 compared to 2.3 ± 0.8 , $p = 0.001$ in the controls. The semi-quantitative assessment of coronary calcification showed no difference between the groups with and without psoriasis, which the authors take to mean no difference in their coronary atherosclerotic burdens.

The author concludes that abnormal MFR is both more common in patients with psoriasis 61% vs 38% in controls and more severe (see authors' Fig. 2).

What can we conclude from the data? As mentioned above, numerous confounders can affect MBF, especially hyperemic flow. Have the authors addressed those? Within the limitations of a retrospective study, the laboratory's extensive database provides a propensity-matched control group that was remarkably similar to the psoriasis group in terms of age, gender, BMI, and the prevalence of traditional risk factors for ischemic heart disease. Even statin use was similar. However, no information is provided regarding the prevalence of other important potential confounders such as use of beta blockers, calcium channel blockers, ACE inhibitors, nitrates and recent caffeine intake, and the prevalence of chronic renal disease.

To what degree did sub-clinical coronary artery disease contribute to the results? Given the presence of any coronary calcium in 52% and severe coronary calcium in 14.5% of the group with psoriasis, some, not insignificant number, of the psoriasis group probably had atherosclerotic coronary artery disease sufficient to affect the MFR. However, the control group was well matched in both the presence and extent of coronary calcium. Could there have been more significant non-calcified plaque in the psoriasis group? Possibly. Resting

heart rate was lower in the psoriasis group but the resting blood flow normalized to double product was no different.

Aside from the missing data on possible confounding drugs, the psoriasis and control groups were as similar as a retrospective study could likely produce. Furthermore, the laboratory at the Brigham has extensive experience with $^{13}\text{NH}_3$ and ^{82}Rb imaging lending credence to the measurements.

Furthermore, within the context of the existing literature, the results make sense. Changes in coronary luminal area by direct angiography and hyperemic PET MBF both measured during cold pressor testing were inversely correlated with the CRP levels.⁶ Hyperemic Doppler coronary flow velocity was reduced in 22% of young patients (mean age 37) with severe psoriasis compared to age- and gender-matched controls. Those with psoriasis and reduced hyperemic flow velocity had higher PASI scores, an index of the severity of disease and in multivariable analysis only the PASI score was a significant determinant of the coronary flow reserve.⁷ PET MBF was measured in 25 patients with systemic lupus erythematosus or rheumatoid arthritis but no coronary risk factors and compared to MBF in healthy volunteers. MFR was significantly lower in the patients with RD compared to the controls.⁸ Furthermore, microvascular dysfunction improves after initiation of anti-inflammatory therapy in patients with rheumatoid arthritis.^{9,10}

The study by Weber et al. adds to a slowly growing body of evidence suggesting that coronary endothelial and/or microvascular dysfunction appears to be a consistent finding in rheumatic diseases. The dysfunction can be correlated to markers of inflammation and is largely independent of traditional risk factors for coronary artery disease. There may be a link between abnormal MFR and the earlier and more severe appearance of clinical atherosclerotic cardiovascular disease in patients with rheumatic disease. Noninvasive studies of myocardial blood flow may additionally be useful for monitoring vascular function during therapy of rheumatic diseases which may, hopefully, be a surrogate for decreasing risk of subsequent cardiovascular events.

Controlled, prospective studies of PET measurements of MBF and MFR and their relationship to long-term outcome would be welcome.

Disclosures

The author has no disclosures related to the content of this editorial.

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